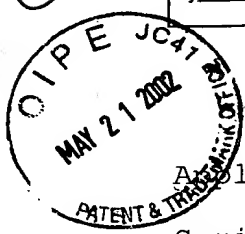


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| CERTIFICATE OF MAILING   |   |
| I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, U.S. Patent and Trademark Office, Box Patents, P.O. box 2327, Arlington, VA 22202-0327, on the date appearing below. |   |
| By <u>Hinda M. Dublin</u>  | ELI LILLY AND COMPANY<br>Date <u>May 15, 2002</u> |



PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

|              |                             |   |                 |
|--------------|-----------------------------|---|-----------------|
| Applicants : | Krushinski, et al.          | ) |                 |
| Serial No. : | 09/890,741                  | ) |                 |
| Filed :      | December 4, 2001            | ) | Group Art Unit: |
|              |                             | ) | 1624            |
| For :        | 5-HT <sub>1F</sub> AGONISTS | ) | Examiner:       |
|              |                             | ) | Sudhaker Patel  |
| Docket No. : | X-11704                     | ) |                 |

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COMMUNICATION

Assistant Commissioner for Patents  
Arlington, VA 22202

Sir:

In a telephone interview with the Examiner, Applicants were notified of an intent to require restriction in the above referenced Application. The proposed restriction would divide the presently claimed invention into compounds of Group I, those compounds wherein R and/or R<sup>1</sup> do not contain a heterocyclic group, and compounds of Group II, those compounds wherein R and/or R<sup>1</sup> contain a heterocyclic group.

Applicants respectfully request reconsideration of any restriction requirement in the present application. It is Applicant's view that all claimed compounds share the same beneficial characteristics as selective 5-HT<sub>1F</sub> agonists useful for activating 5-HT<sub>1F</sub> receptors, inhibiting neuronal protein extravasation, or for the treatment or prevention of migraine. The claimed family of compounds all share the same benzoylpiperidine core with a carbonylamino-linked

substitution at the 3-position of the benzene ring. These compounds are novel and it was surprisingly unexpected that compounds with this core structure and the recited range of substitutions should have selective agonist activity at the 5-HT<sub>1F</sub> receptor.

In addressing the scope of substituents R and R<sup>1</sup> and the intended restriction requirement, and per the Examiner's suggestion, Applicants have reviewed granted patents relating to 5-HT<sub>1F</sub> agonists having substituents defined by Markush groups consisting of both heterocyclic and non-heterocyclic members as examples of similar situations wherein restriction was not required, where, as here, a significant element of the advancement of the invention over the art lay in the discovery of a new core structure having desirable properties. The Examiner suggested that the intended restriction requirement would be reconsidered if such cases were found.

As a result of this review, Applicants wish to bring the following two exemplary cases to the Examiner's attention:

US patent 5,708,008 (Reference AB on Form PTO 1449 submitted herewith, which corresponds to reference BB, EP 0 832 650) claims certain indolylpiperidine compounds as 5-HT<sub>1F</sub> agonists, having carbonylamino linked alkyl and aryl groups (non-heterocycle groups), as well as certain heterocyclic groups as possible substituents at the 6-position of the indole core. No restriction requirement was made in the case. [The Applicants in that case did divide out certain subject matter, which subsequently matured into U.S. patent 5,962,474 (reference AC on Form PTO-1449, submitted herewith), based on the selection of the type of linkage at the 6-position of the indole group, namely thioether or carbonyl linkages, rather than the nitrogen containing linkages claimed in U.S. 5,708,008. This divisional does not appear to have involved a

restriction requirement, and specifically, did not involve a requirement based on whether there were both heterocyclic and non-heterocyclic substituents in a Markush group.]

U.S. patent 5,942,536 (reference AA on the Form PTO-1449 submitted herewith) claims certain other indole compounds as 5-HT<sub>1F</sub> agonists having carbonylamino linked alkyl and aryl groups (non-heterocycle groups), as well as certain heterocyclic groups as possible substituents at the 6-position of the indole core. These Markush groups were not subjected to a restriction requirement in that case.

Additionally, though the compounds claimed in U.S. 5,942,536 do not have a substituted piperidinyl group as in the presently claimed compounds and the compounds claimed in U.S. 5,708,008 described above, they do have a secondary/tertiary amine linked to the 3-position of the indole core and this amine may be substituted with a range of alkyl and aryl groups (non-heterocyclic groups), as well as certain heterocyclic groups. As above, this breadth of Markush group as a substituent on the novel core otherwise claimed, was not subject to a restriction requirement in the application.

[It is acknowledged that an Examiner's Amendment was made in the prosecution of the 5,942,536 patent to cancel claims to subject matter related to a synthetic intermediate and a coupling reagent useful in the synthesis of the claimed 5-HT<sub>1F</sub> agonist compounds. This amendment was agreed to by the Applicants to obviate an intended restriction requirement, which requirement did not relate to the breadth of the Markush groups of the compound claims. The canceled subject matter was subsequently prosecuted in two divisional applications leading to U.S. patents 5,998,630 and 6,126,932. Copies of the front pages and claims of these two patents are enclosed for

the Examiner's convenience. They are not cited on PTO Form 1449 in that they are not considered material to the patentability of the presently claimed invention.]

Lastly, Applicants respectfully note that the present application is a national stage filing of a PCT International application, previously searched and examined by the EPO as the International Searching Authority and International Preliminary Examination Authority. The European counterpart to the above first exemplary patent was cited, along with other references, as "A" references in the International Search Report, i.e. a "document defining the general state of the art which is not considered to be of particular relevance." This same reference, along with others, was cited in the Preliminary Examination Report, which found the claimed class of compounds to be novel and non-obvious. (It is recognized that the EPO Examiner refused to establish a completely positive report on the basis of the scope of the claims in light of European standards for the definiteness of certain types of claim terms, specifically "heteroaryl" and "optionally substituted.") Applicants believe the search report and International Preliminary Examination Reports are part of the record of this PCT National Stage Application, but copies are enclosed herewith for the Examiner's greater convenience.

The above second exemplary patent was not previously cited because its subject matter is not considered material to the patentability of the presently claimed invention, and is in fact further removed in similarity compared to other references previously cited on PTO Form 1449.

In light of the above remarks, Applicants respectfully request reconsideration of the intention to

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require restriction and that the presently claimed invention be searched and examined as a whole.

Respectfully submitted,



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